REMARKS

Reconsideration of this Application is respectfully requested.

Claims 70, 72, 73, 75, 80, 82, 90, 92, 93 have been amended, claims 1-6, 83, 89, 91 stand canceled, claims 7-69, 74, 76-79, 81, 85-88, stand withdrawn, and claims 71, 84, 94, 95 are previously presented. The claims are fully supported by the Application as filed and no new matter has been added.

Based upon the foregoing Amendments and following Remarks, the applicants respectfully request the Examiner reconsider all outstanding objections and rejections, and that they be withdrawn.

Rejection under 35 U.S.C. § 112, first paragraph

Claims 70 -73, 75, 80, 82, 84, 90, 92-95, stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly non-enabled because the claims were directed to stem cells "having an identical pair of one or more alleles." In the Examiner's assessment, the "methodology disclosed and used, parthenogenetically activating an oocyte and generating a cell would result in all the genetic material to be maternal in origin, but would not result in homozygous or identical pairs of chromosomes, or allow for selection of alleles." Applicants respectively disagree.

Nevertheless, Applicants have amended the claims to obviate the allegations of new matter and would like to further observe as follows. The methodology disclosed and used, parthenogenetically activating an oocyte and generating a cell, makes use of the homozygosity in a post-meiosis I germ cell, comprising chromosomes derived from the same homologues. Although the presence of identical pairs of chromosomes in post-meiosis I germ cell is rare and minimal heterozygosity is introduced by recombination events, a great extent of homozygosity remains. Since recombination is prone to occur at some hot spots, a majority of halpotypes are unaffected by recombination and remain homozygous. This knowledge of recombination hot spots plus genotyping technology for haplotype analysis allows for the selection of stem cell

being homozygous on one or more given haplotypes. That being so, it is submitted that the claims are therefore fully enabled and withdrawing of this ground for rejection is respectfully requested.

Beyond that, Applicants believe that the Examiner's arguments seem to indicate a certain degree of incongruency between the Examiner's perception of what the Applicants believe they have invented and what the Examiner understands to be the invention and it is hoped that the following responses to the Examiners remarks would narrow the gap and drive the claims of the present invention to allowability.

The Examiner asserted that "in meiosis there is no duplication of one chromosome resulting two identical or homozygous chromosomes that are segregated during meiosis, thus would not provide for a cell derived from an oocyte that would have such as feature."

Applicants agree that there would be " no duplication of one chromosome resulting two identical or homozygous chromosomes" in meiosis. However, it should be recognized that identical homozygous chromosomes can be obtained, as observed by Kaufman (J. Embryol. exp. Morph. 73, 249-261, 1983), when the extrusion of second polar body is facilitated. The resulting haploid cell become diploid and uniformly homozygous by replicating the haploid chromosome set. This "diplodization" was also observed by Ito et al. (J Exp Zool. 1991 Feb;257(2):178-83. the instant specification includes "homozygous stem cell" derived in this manner (Please see 09/997,240 page 5 line 6).

Thus "homozygous stem cells" of the instant invention although not carrying identical haploid chromosomes, has such a great degree of homozygosity, that it is recognized in the art as virtually, entirely homozygous.

The Examiner further argued that "since the methodology provides no control over genetic recombination, nor the ability to control which chromosome pairs ultimately end up in the resulting cell, there is no reasonable expectation of success based on the guidance of the present specification."

But the instant invention does not aim to control genetic recombination. Rather, the invention uses a post-recombination cell to produce stem cell being homozygous on one or more given haplotypes. Although the methodology of the instant invention does not attempt t o control which chromosome pairs ultimately end up in the resulting cell, it produces stem cell

with a substantial degree of homozygosity than that by natural fertilization and IVF, and it is far superior to any methodology that the inventors are aware of in terms of producing stem cell being homozygous on one or more given haplotypes.

Referring to Cibelli et al, the Examiner expresses doubts as to the viability of the approach of the instant invention. However, Cibelli et al. clearly indicate that the resulting cells are not homozygous, rather considered "autologous" to the oocyte. It should be noticed that in Cibelli et al., the phrase "not homozygous" is not mentioned. "Autologous" is a term used for relation between a cell and a host, not for relation between haplotypes within a cell.

As page 819 of Cibelli et al. describes: "typing for sequence repeats and micro SSPTM generic human lymphocyte antigen class II DNA performed in Cyno-1 cells and somatic cells from donor animal were indistinguishable and therefore should be considered autologous;" the cell Cyno-1 is autologous to the donor animal. The autologous relationship between the cell and the donor animal in Cibelli et al. was used to demonstrate that the cell was derived from the animal. Cibelli et al. did not disclose the status of homozygosity of the Ctno-1 cell, nor the donor host.

Further, the Examiner asserts that "Vrana et al. teach that the resulting cells appear "to be similar to traditional ES cells, it is reasonable to question their viability and utility" (page 11916), since they are derived from only maternal DNA and that impriniting may affect the "Stemness" of the resulting cell (page 11916, second column) when evaluated and compared to other characterized stem cells in the art. Applicants respectfully disagree.

Vrana et al. "questioned" viability and utility of stem cell derived via parthenogenesis, but no evidence was not provided. Various reports on the other hand have supported the stemness and plasticity of such cell. For example, Thomson JA et al.(Genes Dev. 1988 Oct;2(10):1344-51) showed that "Parthenogenetic cells shared a developmental fate similar to gynogenetic cells, contributing to all tissues of the embryo proper and to the extraembryonic mesoderm, but only rarely to the extraembryonic endoderm or to any trophectoderm-derived tissues." Lin et al (Stem Cells. 2003;21(2):152-61) demonstrated that the cell retained a normal karyotype, expressed stage-specific embryonic antigen-1 and Oct4, and were positive for alkaline phosphatase and telomerase. In vivo growth of these cells displayed the development of a variety of tissue types encompassing all three germ layers. In addition, these cells demonstrated the potential for in vitro differentiation into endoderm, neuronal, and hematopoietic lineages.

Rejection under 35 U.S.C. § 112, second paragraph

Previously amended claims 70 – 73, 75, 80, 82, 84, 90, 92 – 95 stand rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicants regard as the invention.

The foregoing arguments and remarks are hereby reiterated. As amended, the claims now refer to stem cells homozygous as to one or more haplotypes. As such, it is respectfully requested that this ground for rejection be withdrawn.

Rejection under 35 U.S.C. § 102 (b)

The Examiner asserts that the Thomson *et al.* reference teaches the isolation and characterization of human embryonic stem cells; that the Doetschman *et al.* reference teaches the isolation and characterization of mouse embryonic stem cells; that the Evans *et al.* reference teaches the isolation and characterization of mouse embryonic stem cells; that the Saito *et al.* reference teaches the isolation and characterization of bovine embryonic stem cells. As such, the Examiner argues that given the broadest reasonable interpretation of the claims of the instant invention, that the above cited references are anticipatory. Applicants disagree.

First, Applicants have amended the claims and ask that the Examiner now give the claims interpretations that are consistent with the scope of the claims as amended, and properly construed, the claims of the instant invention are clearly patentable over the alleged prior art for at least the following reasons.

The Thomson *et al.* reference teaches embryonic stem cell lines derived from human blastocysts using human embryos produced by **in vitro fertilization**. The Doetschman *et al.* reference does not teach **parthenogenetically** created stem cells. The Evans *et al.* reference teaches the establishment in culture of pluripotential cells from mouse embryos derived from pregnant mice **created from fertilization of an oocyte by a sperm**. The Saito *et al.* reference

teaches bovine embryonic stem cell-like cell lines cultured over several passages that were derived from **artificially inseminated** superovulated cows.

In all these cases, the resulting cells would be chromosomally heterozygous. The Examiner's arguments is premised on the fact that it is biologically impossible to produce chromosomally homozygous cells. Although methods encompassing natural fertilization, IVF,... all encompass the use of post-meiosis I diploid germ cell, post-meiosis I diploid germ cell is NOT the only cell used. Natural fertilization, IVF etc still encompass the use of sperm cell giving rise to a heterozygous product whereas the instant invention encompasses the use of post-meiosis I diploid germ cell alone and therefore able to give rise to a homozygous product.

In fact, the post-meiosis I diploid germ cell, as taught in the text book Human Embryology (Larsen), sets forth a distinct structural nature of genome which is predominantly homozygous with extremely minimal heterozygosity introduced by recombination. On page 6, second paragraph of the specification, Applicants explicitly stated that the " the pluripotent stem cells of the present invention are homozygous (with minimal heterozygosity or uniform homozygosity)". Applicants agree that recombination can cause minimal heterozygosity between two haploid chromosome, the resulting genomic structure is for all functional and structural purposes substantially homozygous to a degree that is unmatched by product from natural fertilization or IVF.

Furthermore, the minimal heterozygosity can only be present in the product when the second polar body extrusion is prevented during stem cell derivation. In the instant invention, uniformly homozygosity can be accomplished using the method of allowing the extrusion of the second polar body. When one of the haploid set of chromosomes is extruded as the second polar body, the remaining haploid chromosome can self-replicate and the cell becomes homozygous diploid.

Applicants would admit that although the resulting haploid cells of post-meiosis I do not comprise uniform homozygosity, it would not be appropriate nor acceptable in the relevant scientific community to refer to post-meiosis I germ cell as "not homozygous" or "heterozygous." In fact, as taught in the text book Human Embryology (Larsen), although

recombination occurs, a great degree of homozygosity is remained between the two haploid chromosomes due to the fact that they are derived from the same homologue.

For at least the above considerations, Applicants respectfully assert that there is no basis for maintaining this ground for rejection and respectfully ask that it be withdrawn.

CONCLUSION

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. It is believed that a full and complete response has been made to the outstanding Office action and, as such, the present application is in condition for allowance. Applicants wish to expedite the prosecution process and if the Examiner believes, for any reason that personal communication will help expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Response is respectfully requested.

Respectfully submitted,

REED SMITH, LLP

By: 

Toni-Junell Herbert
Reg. No. 34,348
Chris Aniedobe
Reg. No. 48, 293

Date: 12/19/2006

Reed Smith LLP
3110 Fairview Park Dr.
Suite 1400
Falls Church, VA 22042